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1/77

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15 MAR 2002

Request for grant of a patent

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~~10MAR02 E704108 1 D00524~~
P01/7700 0.00-0206218.0

1.	Your reference	4-32412P1/HO 56
2.	Patent application number *(The Patent Office will fill in this part)*	0206218.0
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

15 MAR 2002

GB0206489.4

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	39
Claim(s)	7
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B. A. Yorke & Co — Date: 15 MAR 2002

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. E. Cheetham** **020 8560 5847**

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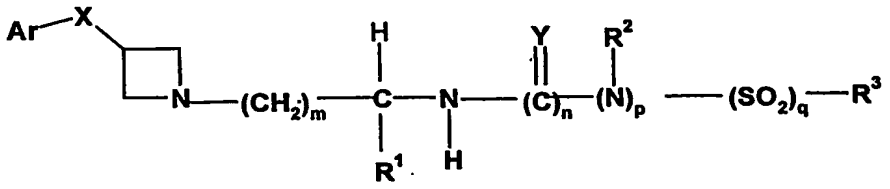
Organic Compounds

This invention relates to organic compounds, their preparation and their use as pharmaceuticals.

In one aspect the invention provides compounds of formula



I

in free or salt form, where

Ar is phenyl optionally substituted by one or more substituents selected from halogen, C_1-C_8-alkyl, cyano or nitro,

R^1 is hydrogen or C_1-C_8-alkyl optionally substituted by hydroxy, C_1-C_8-alkoxy, acyloxy, halogen, carboxy, C_1-C_8-alkoxycarbonyl, -$N(R^4)R^5$, -$CON(R^6)R^7$ or by a monovalent cyclic organic group having 3 to 15 atoms in the ring system,

R^2 is hydrogen or C_1-C_8-alkyl and R^3 is C_1-C_8-alkyl substituted by phenyl, phenoxy, acyloxy or naphthyl, or R^3 is C_3-C_{10}-cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms, phenyl or naphthyl, said phenyl, phenoxy or naphthyl groups being optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, acyl, nitro, C_1-C_8-alkyl, C_1-C_8-haloalkyl, C_1-C_8-alkoxy, C_1-C_8-haloalkoxy, C_1-C_8-alkylthio, C_1-C_8-alkoxycarbonyl, acylamino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino or di(C_1-C_8-alkyl)aminocarbonylmethoxy, or R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which 1, 2 or 3 are hetero atoms,

R^4 and R^5 are each independently hydrogen or C_1-C_8-alkyl, or R^4 is hydrogen and R^5 is hydroxy-C_1-C_8-alkyl, acyl, $-SO_2R^8$ or $-CON(R^6)R^7$, or R^4 and R^5together with the nitrogen atom to which they are attached denote a 5-or 6-membered heterocyclic group,

R^6 and R^7 are each independently hydrogen or C_1-C_8-alkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group,

R^8 is C_1-C_8-alkyl, C_1-C_8-haloalkyl, or phenyl optionally substituted by C_1-C_8-alkyl,

X is $-C(=O)-$, -O-, $-CH_2-$, or CH(OH),

Y is oxygen or sulfur,

m is 1, 2, 3 or 4, and
n, p and q are each 0 or 1, n+p+q=1 or 2, n+q=1, p+q=1, and when n is 0, p is 0.

Terms used in the specification have the following meanings:

"C_1-C_8-alkyl" as used herein denotes straight chain or branched C_1-C_8-alkyl, which may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, or straight or branched octyl. Preferably, C_1-C_8-alkyl is C_1-C_4-alkyl.
"C_3-C_{10}-cycloalkyl" as used herein may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopentyl, cyclohexyl, methylcyclohexyl, dimethylcyclohexyl, cycloheptyl, bicycloheptyl, cyclooctyl, bicyclooctyl, bicyclononyl, tricyclononyl or tricyclodecyl.
"C_1-C_8-alkoxy" as used herein denotes straight chain or branched C_1-C_8-alkoxy which may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, straight or branched pentoxy, straight or branched hexyloxy, straight or branched heptyloxy, or straight or branched octyloxy. Preferably, C_1-C_8-alkoxy is C_1-C_4-alkoxy.
"C_1-C_8-haloalkyl" as used herein denotes C_1-C_8-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.
"C_1-C_8-haloalkoxy" as used herein denotes C_1-C_8-alkoxy as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.
"C_1-C_8-alkylthio" as used herein denotes C_1-C_8-alkyl as hereinbefore defined linked to –S-.

"Acyl" as used herein denotes alkylcarbonyl, for example C_1-C_8-alkylcarbonyl where C_1-C_8-alkyl may be one of the C_1-C_8-alkyl groups hereinbefore mentioned, optionally substituted by one or more halogen atoms; cycloalkylcarbonyl, for example C_3-C_8-cycloalkylcarbonyl where C_3-C_8-cycloalkyl may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; 5- or 6- membered heterocyclylcarbonyl having one or two hetero atoms selected from nitrogen, oxygen and sulfur in the ring, such as furylcarbonyl or pyridylcarbonyl; arylcarbonyl, for example C_6-C_{10}-arylcarbonyl such as benzoyl; or aralkylcarbonyl, for example C_6 to C_{10}-aryl-C_1-C_4-alkylcarbonyl such as benzylcarbonyl or phenylethylcarbonyl. Preferably acyl is C_1-C_4-alkylcarbonyl.

"Acyloxy" as used herein denotes alkylcarbonyloxy, for example C_1-C_8-alkylcarbonyloxy where C_1-C_8-alkyl may be one of the C_1-C_8-alkyl groups hereinbefore mentioned, optionally substituted by one or more halogen atoms; cycloalkylcarbonyloxy, for example C_3-C_8-

cycloalkylcarbonyloxy where C_3-C_8-cycloalkyl may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; 5- or 6- membered heterocyclylcarbonyloxy having one or two hetero atoms selected from nitrogen, oxygen and sulfur in the ring, such as furylcarbonyloxy or pyridylcarbonyloxy; arylcarbonyloxy, for example C_6-C_{10}-arylcarbonyloxy such as benzoyloxy; or aralkylcarbonyloxy, for example C_6 to C_{10}-aryl-C_1-C_4-alkylcarbonyloxy such as benzylcarbonyloxy or phenylethylcarbonyloxy, or aryloxyalkylcarbonyloxy, for example, C_6-C_{10}-aryloxy-C_1-C_8-alkylcarbonyloxy, any of which is optionally substituted in the aryl moiety by at least one substituent selected from C_1-C_8-alkoxy, halogen, C_1-C_8-alkylcarbonyl, aminosulfonyl, C_1-C_8-alkylaminosulfonyl and di(C_1-C_8-alkyl)aminosulfonyl. Preferably acyloxy is C_1-C_4-alkylcarbonyloxy, or benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy optionally substitated in the benzene ring thereof by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl or aminosulfonyl.

"Acylamino" as used herein denotes amino substituted by acyl as hereinbefore defined.

"Halogen" as used herein may be fluorine, chlorine, bromine or iodine; preferably it is fluorine, chlorine or bromine.

"C_1-C_8-alkoxycarbonyl" as used herein denotes C_1-C_8-alkoxy as hereinbefore defined attached through the oxygen atom to a carbonyl group.
"Di-(C_1-C_8-alkyl)aminocarbonylmethoxy" as used herein denotes aminocarbonylmethoxy disubstituted on the amino nitrogen atom by C_1-C_8-alkyl as hereinbefore defined, the two C_1-C_8-alkyl groups being the same or different.

In Ar, the phenyl group may be substituted, for example by one, two or three, preferably one or two halogen atoms, preferably selected from fluorine and chlorine atoms, or by one or two C_1-C_8-alkyl, cyano or nitro groups, or by C_1-C_8-alkyl and one or two halogen, preferably fluorine or chlorine, atoms. When there is one halogen substituent, it is preferably para to the indicated group X. When there are two or three halogen substituents, preferably one is para to the indicated group X and at least one of the others is ortho to the para-halogen substituent.

R^3 as substituted phenyl may, for example, be substituted by one, two, three, four or five, preferably by one, two or three, of the abovementioned substituents. R^3 may be, for example, phenyl substituted by one, two or three substituents selected from halogen, cyano, hydroxy, nitro, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, di(C_1-C_4-alkyl)aminocarbonylmethoxy, C_1-C_4-alkyl,

C_1-C_4-haloalkyl, C_1-C_4-alkylcarbonyl, C_1-C_4-alkylthio, di(C_1-C_4-alkl)amino or C_1-C_4-alkylcarbonylamino. R^3 as substituted phenyl is preferably phenyl substituted by one or more substitutents selected from cyano, halogen, C_1-C_4-alkoxy or di(C_1-C_4-alkyl)aminocarbonylmethoxy, especially cyanophenyl, particularly meta-cyanophenyl, and disubstituted phenyl where one substituent is C_1-C_4-alkoxy or di(C_1-C_4-alkyl)aminocarbonyl-methoxy, preferably ortho to the bond linking R^3 to the remainder of the molecule shown in formula I, and the other, preferably para to the C_1-C_4-alkoxy group, is C_1-C_4-alkoxy, halogen, cyano or C_1-C_4-alkyl.

When R^3 is C_1-C_4-alkyl substituted by optionally substituted phenoxy, the substitutent(s) on phenoxy may be, for example, one, two or three substituents selected from halogen, cyano, C_1-C_8-alkyl, C_1-C_8-alkoxy or C_1-C_8-alkylcarbonyl.

R^3 as a heterocyclic group may be, for example, a group having 5 to 11 ring atoms of which one, two, three or four, preferably one or two, are hetero atoms selected from nitrogen, oxygen or sulfur, such as pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, tetrazolyl, pyridyl, pyranyl, pyrazinyl, or a 5-, 6- or 7-membered heterocyclic, ring preferably having one or two oxygen or nitrogen ring atoms, fused to a benzene ring, said heterocyclic group being optionally substituted by halogen, C_1-C_4-alkyl or phenyl-C_1-C_4-alkyl.

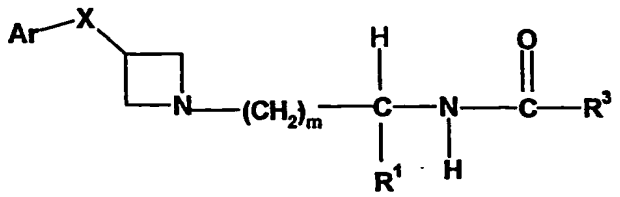
R^2 and R^3 together with the nitrogen atom to which they are attached as a heterocyclic group may be, for example, a group having a 5- or 6-membered ring of which one, two or three are heteroatoms, optionally fused to a benzene ring, such as piperidyl, piperazinyl, morpholino, or benzopiperidyl, optionally substituted by one or more substituents selected from C_1-C_8-alkyl, C_1-C_8-alkoxy or halogen.

R^1 as optionally substituted C_1-C_8-alkyl is preferably optionally substituted C_1-C_4-alkyl, especially C_1-C_4-alkyl or substituted methyl or ethyl. When R^1 is substituted by a cyclic organic group, the latter may be a carbocyclic or heterocyclic group, for example a C_3-C_{15}-carbocyclic group or a 5- to 7-membered heterocyclic group having one or more, preferably one, two or three, ring hetero atoms selected from nitrogen, oxygen and sulfur. The C_3-C_{15}-carbocyclic group may be, for example, a cycloaliphatic group having 3 to 8 carbon atoms, preferably C_5 - or C_6 - cycloalkyl such as cyclopentyl, methylcyclopentyl or cyclohexyl. The C_3-C_{15}-carbocyclic group may alternatively be, for example, a C_6-C_{15} aromatic group, such as phenyl, which is unsubstituted or substituted by C_1-C_8-alkyl, C_1-C_8-alkoxy, halogen, cyano, -CON(R^4)R^5, -

$SO_2N(R^4)R^5$ or C_1-C_8-alkylsulfonylamino where R^4 and R^5 are as hereinbefore defined. The heterocyclic group may have one nitrogen, oxygen or sulfur atom in the ring or it may have two nitrogens, or one oxygen and one or two nitrogens, or one sulfur and one or two nitrogens in the ring. The heterocyclic group is preferably a heterocyclic aromatic group, especially a 5- or 6- membered heterocyclic group such as furyl, imidazolyl, thiazolyl or pyridyl. Preferred embodiments include those in which R^1 is hydrogen or C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy.

Preferred compounds of formula I in free or salt form include those in which
Ar is phenyl substituted by one or two substituents selected from fluorine and chlorine,
R^1 is hydrogen, C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy, C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or C_1-C_4-alkyl substituted by naphthyl,
R^2 is hydrogen or C_1-C_4-alkyl, and R^3 is C_1-C_4-alkyl substituted by phenyl or phenoxy, or C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or C_1-C_4-alkyl substituted by naphthyl, or R^3 is C_5-C_8-cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which one or two are hetero atoms, selected from nitrogen, oxygen or sulfur, phenyl or naphthyl, said phenyl, phenoxy and naphthyl groups being optionally substituted by one, two or three substituents selected from halogen, cyano, nitro, hydroxy, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl, C_1-C_4-alkylthio, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylcarbonylamino, or R^2 and R^3, together with the nitrogen atom to which they are attached, denote a heterocyclic group having a N-heterocyclic ring optionally fused to a benzene ring.
X is –O-, -C(=O)- or -CH_2-,
Y is oxygen and
m is 2, 3 or 4.

Especially preferred compounds of formula I in free or salt form include compounds of formula



II

where

Ar is phenyl substituted by one or two substituents selected from fluorine and chlorine, one of said substituents being para to the indicated group X,

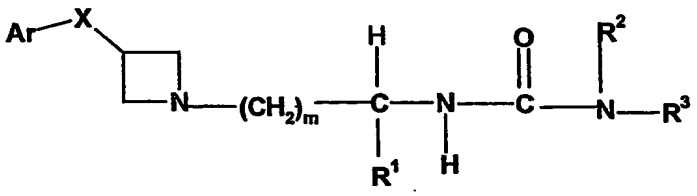
R^1 is hydrogen, C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy, C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or C_1-C_4-alkyl substituted by naphthyl,

R^3 is phenyl substituted by one, two or three substituents selected from halogen, cyano, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylcarbonylamino or C_1-C_4-alkoxy, or R^3 is naphthyl optionally substituted by fluorine, or R^3 is C_1-C_4-alkyl substituted by phenoxy which is optionally substituted by one or two substituents selected from halogen, cyano, C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-alkylcarbonyl, or R^3 is C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or R^3 is a heterocyclic group having a 5- or 6-membered heterocyclic ring in which one or two ring atoms are hetero atoms selected from nitrogen, oxygen and sulfur optionally fused to a benzene ring which is optionally substituted by one or two substituents selected from halogen, C_1-C_4-alkoxy and C_1-C_4-alkylcarbonyl,

X is –O-, and

m is 2 or 3.

compounds of formula



III

where

Ar is phenyl substituted by one or two substituents selected from fluorine and chlorine, one of said substituents being para to the indicated group X,

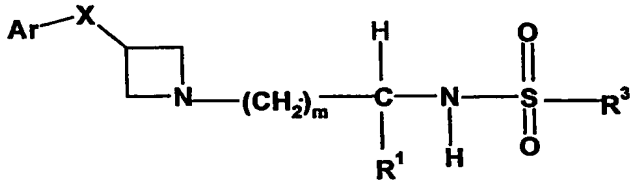
R^1 is hydrogen, C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy,

R^2 is hydrogen or C_1-C_4-alkyl and R^3 is C_5-C_9-cycloalkyl, a heterocyclic group having 5 to 11 ring atoms of which one or two are nitrogen or oxygen atoms, phenyl optionally substituted by one, two or three substituents selected from fluorine, chlorine, hydroxy, nitro, C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxy, phenyl-C_1-C_4-alkyl substituted in the phenyl group by one or two substituents selected from halogen and C_1-C_4-alkyl, C_1-C_4-alkyl substituted by naphthyl, or C_5-C_6-cycloalkyl having a benzo group fused thereto, or R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group having a 6-membered N-heterocyclic ring fused to a benzene ring which is optionally substituted by up to 2 C_1-C_4-alkoxy groups,

X is -O- or -C(=O)-, and

m is 2 or 3.

and compounds of formula



IV

where

Ar^1 is phenyl substituted by one or two substituents selected from fluorine and chlorine, one of said substituents being para to the indicated group X,

R^1 is hydrogen or C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy,

R^3 is phenyl optionally substituted by halogen, C_1-C_4-alkyl or cyano, or R^3 is an aromatic N- or S-heterocyclic group having 5 to 10 ring atoms, or R^3 is phenyl-C_1-C_4-alkyl,

X is –O- and

m is 2 or 3.

The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid,

dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

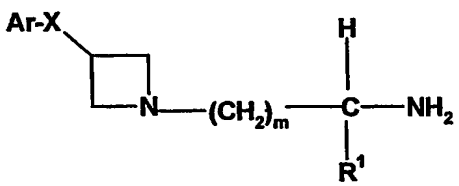
Compounds of formula I which contain acidic, e.g. carboxyl, groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

When R^1 is other than hydrogen, the carbon atom to which R^1 is attached in formula I is asymmetric, in which case the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The invention embraces both individual optically active R and S isomers as well as mixtures, e.g.racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

The invention also provides a process for the preparation of compounds of formula I which comprises

(i) (A) for the preparation of compounds of formula I where n is 1 and p is 1, reacting a compound of formula



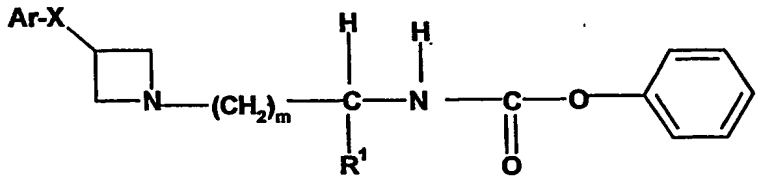
V

with a compound of formula

$$Y{=}C{=}N{=}R^3 \qquad \text{VI}$$

where Ar, R^1, R^3, X, Y and m are as hereinbefore defined, with the proviso that when R^1 contains a reactive functional group it may be in protected form, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen, or

(B) for the preparation of compounds of formula I where n is 1, p is 1 and R^2 is hydrogen or C_1-C_8-alkyl, reacting a compound of formula



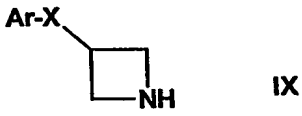
VII

with a compound of formula

$$R^2NHR^3 \qquad \text{VIII}$$

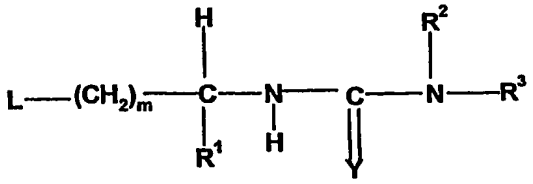
where Ar, R^1, R^2, R^3 and m are as hereinbefore defined, or and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen, or

(C) for the preparation of compounds of formula I where n is 1, p is 1 and R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group, reacting a compound of formula



IX

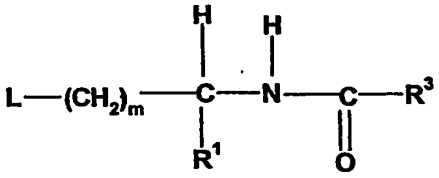
with a compound of formula



X

where Ar, R^1, Y and m are as hereinbefore defined, R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which one, two or three are hetero atoms, and L is halogen, preferably bromine, or

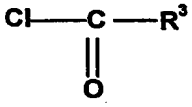
(D) for the preparation of compounds of formula I when n is 1, p is 0, R^2 is hydrogen and Y is oxygen, reacting a compound of formula IX with a compound of formula



XI

where R^1, R^3, L and m are as hereinbefore defined, or

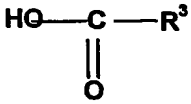
(E) for the preparation of compounds of formula I where n is 1, p is 0, R^2 is hydrogen and Y is oxygen, reacting a compound of formula V with a compound of formula



XII

where R^3 is as hereinbefore defined, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen, or

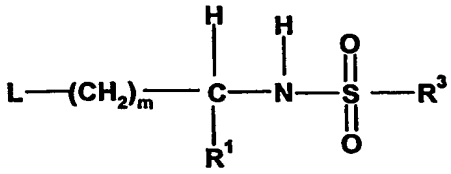
(F) for the preparation of compounds of formula I where n is 1, p is 0, R^2 is hydrogen and Y is oxygen, reacting a compound of formula V with a compound of formula



XIII

where R^3 is as hereinbefore defined, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen or

(G) for the preparation of compounds of formula I where n is 0, p is 0, and q is 1, reacting a compound of formula IX in the form of a hydrohalide salt with a compound of formula



XIV

where R^1, R^3, L and M are as hereinbefore defined, and

(ii) recovering the product in free or salt form.

Process variant (A) may be effected using known procedures for reaction of amines with isocyanates or analogously e.g. as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent, for example a halohydrocarbon such as dichloromethane (DCM) or an ether such as dioxane. The reaction temperature may be e.g. from 0 °C to 100 °C, conveniently ambient temperature.

Process variant (B) may be effected using known procedures for reaction of carbamic acid phenyl esters with amines or analogously e.g. as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent such as dimethyl sulfoxide (DMSO). The reaction temperature may be e.g. from 0 to 100 °C, conveniently ambient temperature.

Process variant (C) may be effected using known procedures for reaction of heterocyclic secondary amines with haloalkylureas or analogously e.g. as hereinafter described in the Examples. The reaction is usually effected between the hydrochloride salt of the compound of formula IX and the compound of formula X in the presence of a tertiary amine. The reaction is conveniently effected in an organic solvent, e.g. a halohydrocarbon such as DCM. The reaction temperature may be e.g. from 0 to 100 °C, conveniently ambient temperature.

Process variant (D) may be effected using known procedures for reaction of heterocyclic secondary amines with N-(haloalkyl) amides or analogously e.g. as hereinafter described in the Examples. It is usually effected between the hydrochloride salt of the compound of formula IX and the compound of formula XI in the presemce of a tertiary amine. Reaction is

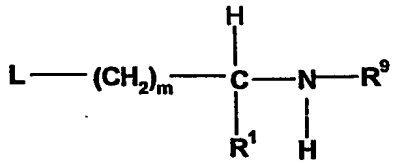
conveniently effected in an organic solvent such as acetonitrile. The reaction temperature may be e.g. from 0 to 100 °C, conveniently ambient temperature.

Process variant (E) may be effected using known procedures for amide-forming reaction of amines with acid halides or analogously. Process variant (F) may be effected using known procedures for amide formation, for example by reaction in the presence of a tertiary amine and a peptide compiling agent, conveniently in an organic solvent, e.g. a halohydrocarbon such as DCM. The reaction temperature may be e.g. from 0 to 40°C, conveniently ambient temperature.

Process variant (G) may be effected using known procedures for reaction of heterocyclic secondary amines with N-(haloalkyl) sulfonamides or analogously e.g. as hereinafter described in the Examples. It is usually effected in the presence of a tertiary amine, conveniently in an organic solvent such as acetonitrile. The reaction temperature may be e.g. from 0 to 100 °C, conveniently ambient temperature.

Compounds of formula V may be prepared by reacting a compound of formula IX

with a compound of formula



XV

where R^1, L and m are as hereinbefore defined, with the proviso that when R^1 contains a reactive functional group such as a hydroxy group, the reactive group may be in protected form, for example a hydroxy group protected as a tert-butoxy group, and R^9 is hydrogen or an amine-protective group, for example a tert-butoxycarbonyl group, and, where R^9 is a protective group, replacing R^9 in the product by hydrogen, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen. When R^9 is hydrogen, reaction between a compound of formula XV and a salt of a compound of formula IX may be effected by the procedures described in US4559349. When R^9 is a protective group, reaction between compounds of formulae XV and IX may be effected using known methods, for example in the presence of a tertiary organic base such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), conveniently in an inert organic solvent, for example a

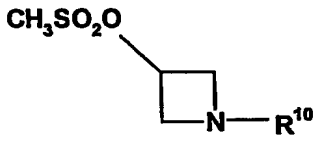
polar solvent such as dimethylformamide, the reaction temperature suitably being from 0 to 40°C, preferably ambient temperature. Replacement of a protective group R^9 by hydrogen may be effected using known procedures; for example, where R^9 is tert-butoxycarbonyl, by treatment with a carboxylic acid such as trifluoroacetic acid. Replacement of a protecting group in R^1 may be affected using known procedures, for example, when R^1 contains a hydroxy group protected as an ether group, such as tert-butoxy, by treatment with HBr in a carboxylic acid such as acetic acid; when R^9 is a protective group, this treatment also replaces R^9 by hydrogen.

Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wuts, John Wiley & Sons Inc, Second Edition, 1991, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen.

Compounds of formulae VI and VIII are commercially available or may be prepared by known methods.

Compounds of formula VII may be prepared by reacting a compound of formula V with phenyl chloroformate in the presence of a base such as a tertiary amine, for example as hereinafter described in the Examples.

Compounds of formula IX where X is –O- may be prepared by reacting a compound of formula

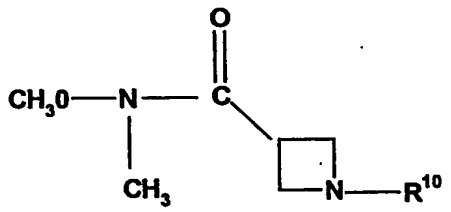


XVI

with a compound of formula Ar-OH in the presence of sodium hydride, where Ar is as hereinbefore defined and R^{10} is a protecting group, and replacing R^{10} in the product by hydrogen. The reaction may be carried out in an inert organic solvent such as DMF. Suitable reaction temperatures may be from 20°C to 150°C, conveniently from 50 to 70°C. The replacement of R^{10} by hydrogen may be affected using known procedures, for example where R^{10} is benzhydryl by reacting the product of the reaction of the compound of formula XVI and

Ar^1-OH with 1-chloroethyl chloroformate, a suitable reaction tempterature being 10-30°C, conveniently at room temperature.

Compounds of formula IX where X is –C(=O)- may be prepared by reacting a compound of formula

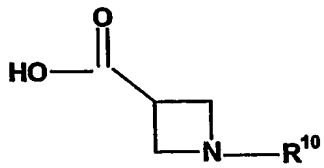


XVII

with a compound of formula

XVIII

where Ar and R^{10} are as hereinbefore defined, and replacing R^{10} in the product by hydrogen. Reaction of compounds of formulae XVII and XVIII may be effected in an inert organic solvent, e.g. an ether such as THF and/or diethyl ether; suitable reaction temperatures may be from -10°C to 10°C, conveniently from –5 to 5°C. Replacement of R^{10} in the product by hydrogen may be effected as hereinbefore described. Compounds of formula XVII may be prepared by reacting a compound of formula

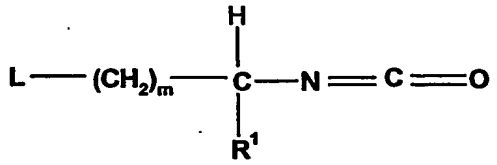


XIX

with O, N-dimethylhydroxylamine hydrochloride in the presence of a peptide coupling agent such as di-imidazol-l-yl-methanone, conveniently in an inert organic solvent such as THF, suitably at reflux temperature. Compounds of formulae XVIII and XIX are known or may be prepared using known procedures.

Compounds of formula IX where X is $-CH_2-$ may be prepared by reduction of compounds of formula IX where X is –C(=O) –, for example using known reduction procedures.

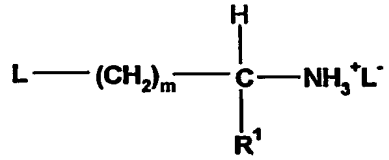
Compounds of formula X may be prepared by reaction of a compound of formula



XX

with a compound of formula H-N(R^2)R^3 where L, R^1, R^2 and R^3 are as defined in formula X, for example as hereinafter described in the Examples.

Compounds of formula XI may be prepared by reaction of a compound of formula



XXI

with a compound of formula XIII, for example as hereinafter described in the Examples.

Compounds of formula XIV may be prepared by reacting a compound of formula XXI with a compound of formula R^3SO_2Cl, for example as hereinafter described in the Examples.

Compounds of formulae XII, XIII, XV, XVI, XX and XXI are known or may be prepared by known procedures.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallization or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula I in free or pharmaceutically acceptable salt form, hereinafter referred to alternatively as agents of the invention, are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free or pharmaceutically acceptable salt form for use as a pharmaceutical. The agents of the invention act as CCR-3 receptor antagonists, thereby inhibiting the infiltration and activation of inflammatory cells, particularly eosinophils, and inhibiting allergic response. The inhibitory properties of agents of the invention can be demonstrated in the following assay :

CCR-3 Binding Assay

In this assay the effect of agents of the invention on the binding of human eotaxin to human CCR-3 is determined. Recombinant cells expressing human CCR-3 are captured by wheatgerm agglutinin (WGA) polyvinyltoluidene (PVT) SPA beads (available from Amersham), through a specific interaction between the WGA and carbohydrate residues of glycoproteins on the surface of the cells. [^{125}I]-human eotaxin (available from Amersham) binds specifically to CCR-3 receptors bringing the [^{125}I]-human eotaxin in close proximity to the SPA beads. Emitted â-particles from the [^{125}I]-human eotaxin excite, by its proximity, the fluorophore in the beads and produce light. Free [^{125}I]-human eotaxin in solution is not in close proximity to the scintillant and hence does not produce light. The scintillation count is therefore a measure of the extent to which the test compound inhibits binding of the eotaxin to the CCR-3.

Preparation of Assay Buffer: 5.96 g HEPES and 7.0 g sodium chloride are dissolved in distilled water and 1M aqueous $CaCl_2$ (1 mL) and 1M aqueous $MgCl_2$ (5 mL) are added. The pH is adjusted to 7.6 with NaOH and the solution made to a final volume of 1 L using distilled water. 5 g bovine serum albumin and 0.1 g sodium azide are then dissolved in the solution and the resulting buffer stored at 4°C. A Complete™ protease inhibitor cocktail tablet (available from Boehringer) is added per 50 mL of the buffer on the day of use.

Preparation of Homogenisation Buffer: Tris-base (2.42g) is dissolved in distilled water, the pH of the solution is adjusted to 7.6 with hydrochloric acid and the solution is diluted with distilled water to a final volume of 1L. The resulting buffer is stored at 4°C. A Complete™ protease inhibitor cocktail tablet is added per 50 mL of the buffer on the day of use.

Preparation of membranes: Confluent rat basophil leukemia (RBL-2H3) cells stably expressing CCR3 are removed from tissue culture flasks using enzyme-free cell dissociation buffer and resuspended in phosphate-buffered saline. The cells are centrifuged (800 g, 5 minutes), the pellet resuspended in ice-cold homogenisation buffer using 1 mL homogenisation buffer per gram of cells and incubated on ice for 30 minutes.The cells are homogenised on ice with 10

strokes in a glass mortar and pestle.The homogenate is centrifuged (800 g, 5 minutes, 4°C), the supernatant further centrifuged (48,000 g, 30 minutes, 4°C) and the pellet redissolved in Homogenisation Buffer containing 10% (v/v) glycerol.The protein content of the membrane preparation is estimated by the method of Bradford (Anal.Biochem. (1976) 72:248) and aliquots are snap frozen and stored at –80°C.

The assay is performed in a final volume of 250 µL per well of an Optiplate (ex Canberra Packard). To selected wells of the Optiplate are added 50 µL of solutions of a test compound in Assay Buffer containing 5 % DMSO (concentrations from 0.01nM to 10 µM). To determine total binding, 50 µL of the Assay Buffer containing 5 % DMSO is added to other selected wells. To determine non-specific binding, 50 µL of 100nM human eotaxin (ex R&D Systems) in Assay Buffer containing 5 % DMSO is added to further selected wells. To all wells are added 50 µL [^{125}I]-Human eotaxin (ex Amersham) in Assay Buffer containing 5 % DMSO at a concentration of 250 pM (to give a final concentration of 50 pM per well), 50 µL of WGA-PVT SPA beads in Assay Buffer (to give a final concentration of 1.0mg beads per well) and 100 µL of the membrane preparation at a concentration of 100 µg protein in Assay Buffer (to give a final concentration of 10 µg protein per well). The plate is then incubated for 4 hours at room temperature. The plate is sealed using TopSeal-S (ex Canberra Packard) according to the manufacturer's instructions. The resulting scintillations are counted using a Canberra Packard TopCount, each well being counted for 1 minute. The concentration of test compound at which 50% inhibition occurs (IC_{50}) is determined from concentration-inhibition curves in a conventional manner.

The compounds of the Examples hereinbelow generally have IC_{50} values below 1µM in the above assay. For instance, the compounds of Examples 16, 21, 26, 29, 37, 45 and 47 have IC_{50} values of 0.1µM, 0.01µM, 0.01µM, 0.02µM, 0.02µM, 0.01µM and 0.03µM respectively.

Most of the compounds of the Examples exhibit selectivity for inhibition of CCR-3 binding relative to inhibition of binding of the alpha-1 adrenergic receptor.The inhibitory properties of agents of the invention on binding of the alpha-1 adrenergic receptor can be determined in the following assay:

Cerebral cortices from male Sprague-Dawley rats (175-200 g) are dissected and homogenised in 10 volumes of ice cold 0.32 M sucrose (containing 1mM $MgCl_2$ dihydrate and 1mM K_2HPO_4) with a glass/teflon homogeniser. The membranes are centrifuged at 1000 x g for 15 miN, the pellet discarded and the centrifugation repeated. The supernatants are pooled and centrifuged at 18,000 x g for 15 min. The pellet is osmotically shocked in 10 volumes of water

and kept on ice for 30 min. The suspension is centrifuged at 39,000 x g for 20 min, resuspended in Krebs-Henseleit buffer pH 7.4 (1.17mM $MgSO_4$ anhydrous, 4.69 mM KCl, 0.7mM K_2HPO_4 anhydrous, 0.11M NaCl, 11 mM D-glucose and 25 mM $NaHCO_3$) containing 20mM Tris, and kept for 2 days at -20°C. The membranes are then thawed at 20-23°C, washed three times with Krebs-Henseleit buffer by centrifugation at 18,000 x g for 15 min, left overnight at 4°C and washed again three times. The final pellet is resuspended with a glass/teflon homogeniser in 125mL/100 membranes in the same buffer. A sample is taken to determine the protein concentration (using the Bradford Assay with gamma globulin as the standard) and the remainder aliquoted and stored at -80°C.

The resulting membranes are subjected to a radioligand binding assay. The assay is conducted in triplicate using 96 well plates containing [^{125}I]-HEAT (Amersham) (40pM, K_d: 58.9 ± 18.7 pM), unlabelled test compound and membrane (57.1µg/mL) to yield a final volume of 250µL (assay buffer containing 50 mM Tris-base and 0.9% (w/v) NaCl, pH 7.4). The plates are incubated at 37°C for 60 min, after which rapid vacuum filtration over Whatman GF/C 96 well filter plates is carried out. Each plate is then washed three times with 10ml of ice cold assay buffer using a Brandel Cell harvester (Gaithersburg, MD). Following drying of the plates for 3 h. at 50°C, 40 µL of Microscint 20 is added to each well, the plates incubated at room temperature for a further 20 min and the retained radioactivity quantified in a Packard Topcount NXT scintillation counter.

Stock solutions of test compounds are dissolved initially in 100 % DMSO and diluted with assay buffer to the required concentrations to yield 1 % (v/v) DMSO.

The concentration of test compound at which 50% inhibition occurs (IC_{50}) is determined from concentration-inhibition curves in a conventional manner.

Having regard to their inhibition of binding of CCR-3, agents of the invention are useful in the treatment of conditions mediated by CCR-3, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, bronchial hyperreactivity, remodelling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, excercise-induced asthma, occupational asthma and asthma induced following bacterial or viral infection. Treatment of asthma is also

to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute/adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including

hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

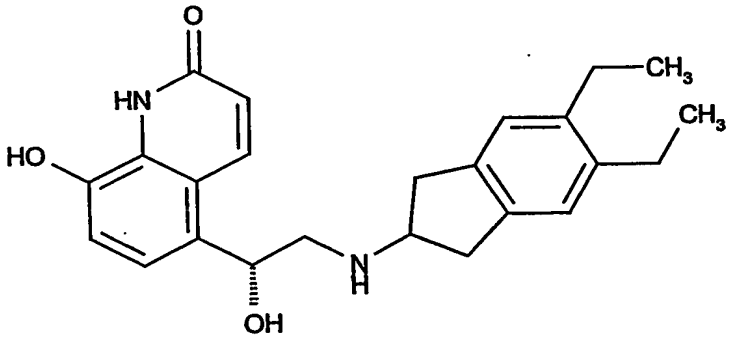
Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, e.g. atrophic, chronic, or seasonal rhinitis, inflammatory conditions of the gastrointestinal tract, for example inflammatory bowel disease such as ulcerative colitis and Crohn's disease, diseases of the bone and joints including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and systemic sclerosis, and other diseases such as atherscleroSis, multiple sclerosis, diabetes (type I), myasthenia gravis, hyper IgE syndrome and acute and chronic allograft rejection, e.g. following transplantation of heart, kidney, liver, lung or bone marrow.

The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. CliN Invest. (1995) 96:2924-2931; and Cernadas et al (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such

drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, LTB4 antagonists such as those described in US5451700, LTD4 antagonists such as montelukast and zafirlukast, dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]-amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca), and PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), and PD189659 (Parke-Davis). Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, and beta-2 adrenoceptor agonists such as salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International Publication No. WO00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride. Combinations of agents of the invention and steroids, beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

Other useful combinations of agents of the invention with anti-inflammatory drugs are those with other anatagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzocyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770), CCR-5 antagonists described in US6166037 (particularly claims 18 and 19), WO00/66558 (particularly claim 8), and WO00/66559 (particularly claim 9).

In accordance with the foregoing, the invention also provides a method for the treatment of a condition mediated by CCR-3, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof an effective amount of a compound of formula I in a free or pharmaceutically acceptable salt form as hereinbefore described. In another aspect the invention provides the use of a compound of formula I, in free or pharmaceutically acceptable salt form, as hereinbefore described for the manufacture of a medicament for the treatment of a condition mediated by CCR-3, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; by inhalation, for example in the treatment of inflammatory or obstructive airways disease; intranasally, for example in the treatment of allergic rhinitis; topically to the skin, for example in the treatment of atopic dermatitis; or rectally, for example in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising as active ingredient a compound of formula I in free or pharmaceutically acceptable salt form, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent such as an anti-inflammatory bronchodilatory or antihistamine drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions

for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

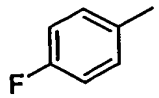
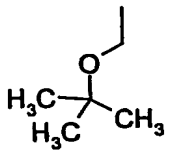
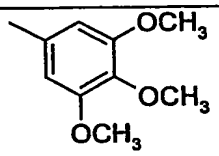
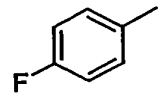
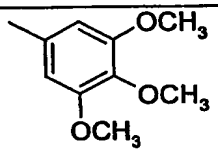
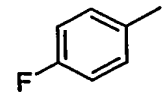
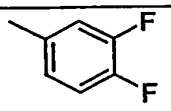
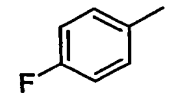
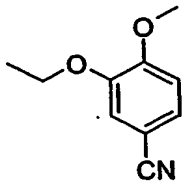
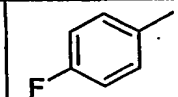
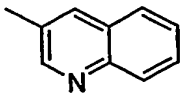
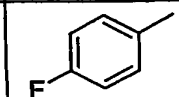
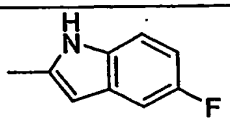
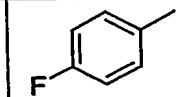
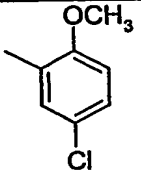
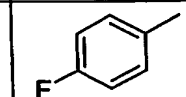
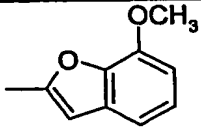
The invention includes (A) an agent of the invention in inhalable form, e.g. in an aerosol or other atomisable composition or in inhalable particulate, e.g. micronised form, (B) an inhalable medicament comprising an agent of the invention in inhalable form; (C) a pharmaceutical product comprising such an agent of the invention in inhalable form in association with an inhalation device; and (D) an inhalation device containing an agent of the invention in inhalable form.

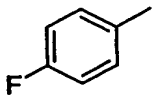
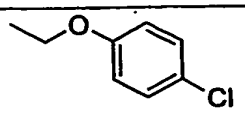
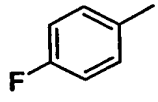
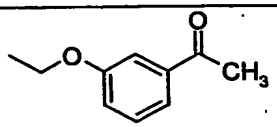
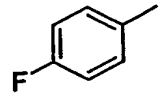
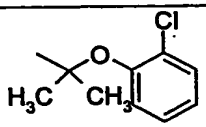
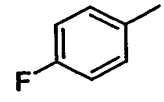
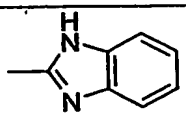
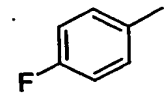
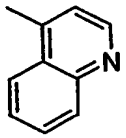
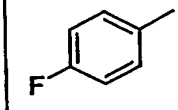
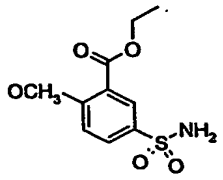
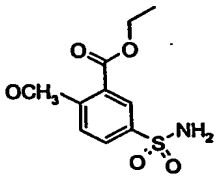
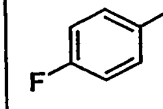
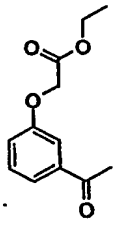
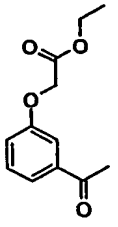
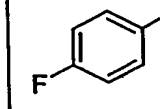
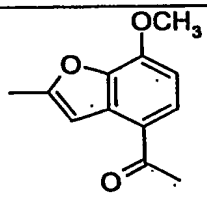
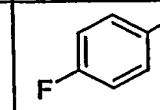
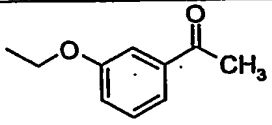
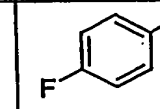
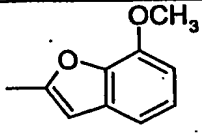
Dosages of agents of the invention employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.01 to 30 mg/kg while for oral administration suitable daily doses are of the order of 0.01 to 100 mg/kg.

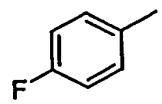
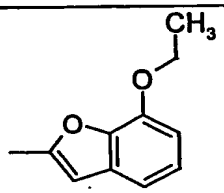
The invention is illustrated by the following Examples.

Examples 1 - 19

Compounds of formula II are shown in the following table, the methods of preparation being described hereinafter. The table also shows characterising mass spectrometry data. X is O except in Example 7 where it is C=O. The value of m in formula II is 2. The compounds are all in free form.

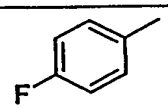
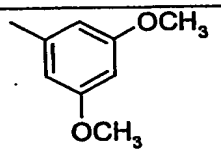
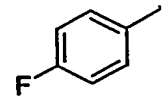
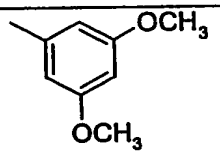
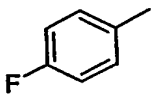
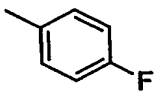
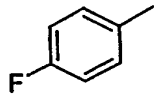
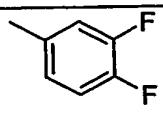
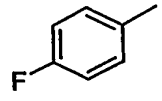
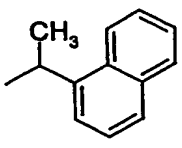
Ex No.	Ar	R^1	R^3	MS [M+H]
1				505.3
2				449.1
3				
4		H		414.1
5		H		380.1
6		H		386.1
7		H		405.0
8		H		399.1

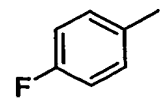
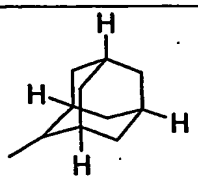
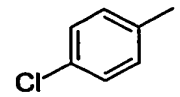
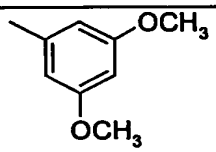
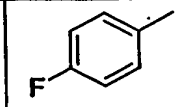
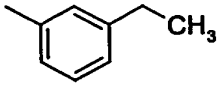
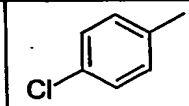
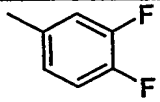
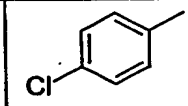
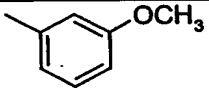
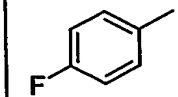
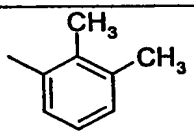
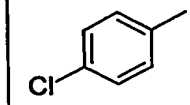
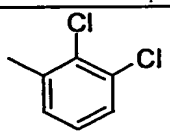
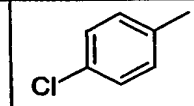
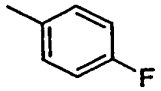
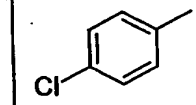
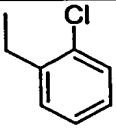
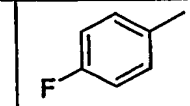
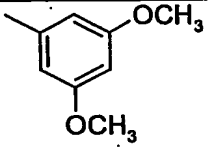
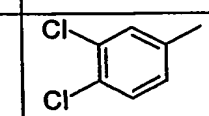
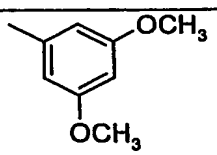
9		H		393.1
10		H		401.1
11		H		421.1
12		H		369.1
13		H		380.0
14				681.4
15				607.3
16		H		442.2
17				431.2
18				428.8

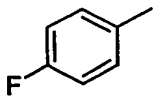
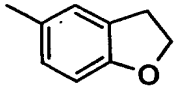
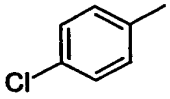
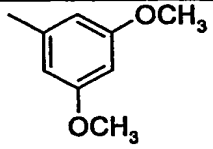
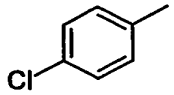
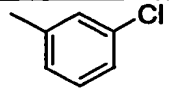
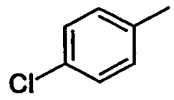
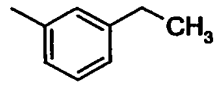
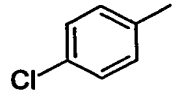
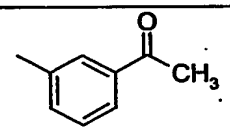
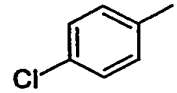
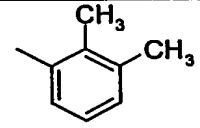
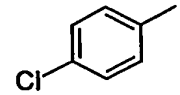
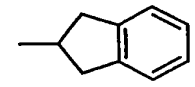
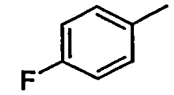
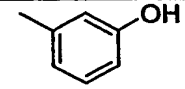
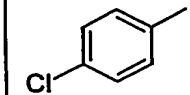
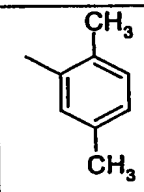
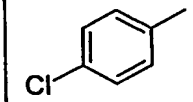
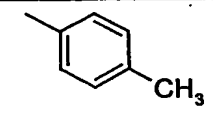
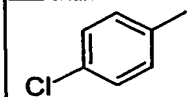
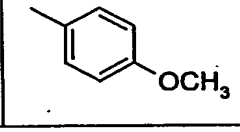
19		H		412.5 [M+]

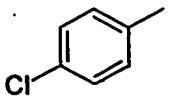
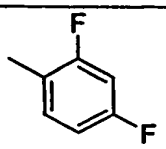
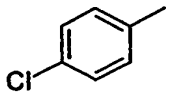
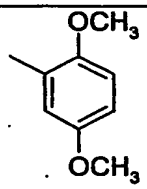
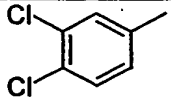
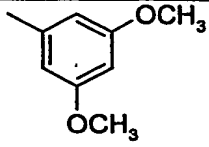
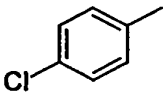
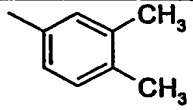
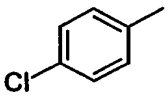
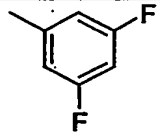
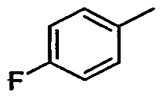
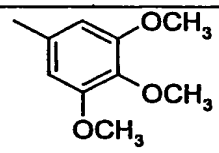
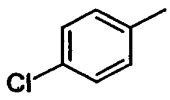
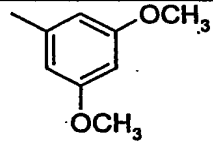
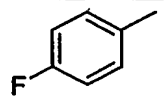
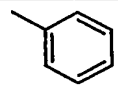
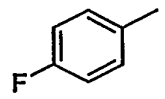
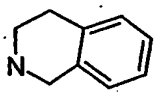
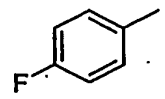
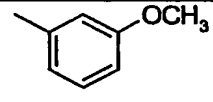
Examples 20 - 57

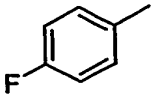
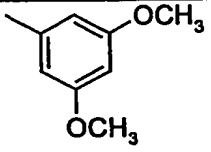
Compounds of formula III are shown in the following table, the methods of preparation being described hereinafter. The table also shows characterising mass spectrometry data. X is O except in Examples 34, 37 and 49, where it is C=O. R^2 is hydrogen except in Example 54 where it is CH_3, and in Example 55 where R^2 and R^3 together with the attached nitrogen atom denote the group shown in the R^3 column. The value of m in formula III is 2 for Examples 20-56 and 3 for Example 57. Examples 24-25, 27, 29-33 and 36 are in the form of the trifluoroacetate salt; the others are in free form.

Ex. No	Ar	R^1	R^3	MS [M+H]
20		H		404.1
21		CH_2OH		434.1
22		H		362.1
23		H		380.1
24		H		422.1

25		H		402.2
26		CH_2OH		450.0
27		H		372.2
28		CH_2OH		426.2
29		CH_2OH		420.2
30		H		372.2
31		CH_2OH		458.2
32		CH_2OH		408.2
33		CH_2OH		438.2
34		CH_2OH		446.1
35		CH_2OH		484.0

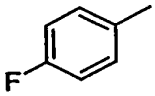
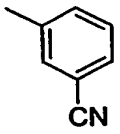
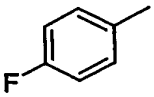
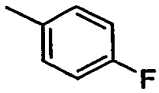
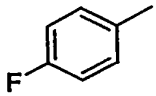
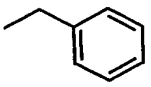
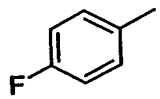
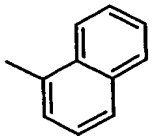
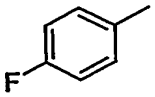
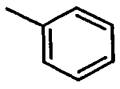
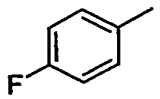
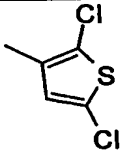
36		H		386.1
37		CH_2OH		461.8
38		CH_2OH		423.6
39		CH_2OH		417.5
40		CH_2OH		431.7
41		CH_2OH		418.0
42		CH_2OH		429.9
43		H		360.1
44		CH_2OH		418.0
45		CH_2OH		403.6
46		CH_2OH		419.8

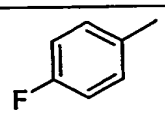
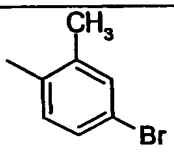
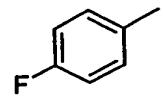
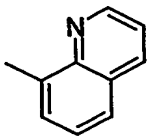
47		CH_2OH		425.5
48		CH_2OH		449.9
49		CH_2OH		495.6
50		CH_2OH		417.8
51		CH_2OH		425.7
52		CH_2OH		464.2
53		H		420.1
54		H		364.0
55		H	 (R^2 + R^3)	384.1
56		H		374.0

57		H		417.5

Examples 58 - 65

Compounds of formula IV are shown in the following table, the methods of preparation being described hereinafter. The table also shows characterising mass spectrometry data. The value of m in formula IV is 2 in all of these Examples, R^1 is hydrogen and X is O. The compounds are all in free form.

Ex. No	Ar	R^3	MS [M+H]
58			390.0
59			383.0
60			379.0
61			415.1
62			365.0
63			440.7

64			457.37
65			415.49

1-[(S)-3-[3-(4-Chloro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(3,5-dimethoxy-phenyl)-urea – Example 26

(S)-2-tert-Butoxycarbonylamino-4-[3-(4-chloro-phenoxy)-azetidin-1-yl]-4-oxo-butyric acid benzyl ester

A solution of (S)-2-tert-butoxycarbonylamino-succinic acid 1-benzyl ester 5.0g, 13.99mmol) in dichloromethane (50ml) is treated with diisopropylethlyamine (7.51ml, 41.97mmol) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (4.49g, 13.99mmol). To the reaction mixture is added 3-(4-chloro-phenoxy)-azetidine hydrochloride (3.06g, 13.99mmol) and stirring continued for 3 hours. The dichloromethane is evaporated and residue partioned between ethylacetate and saturated aqueous $NaHCO_3$. The ethylacetate phase is washed with 1M HCl solution and brine, dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution with 1:1 ethylacetate/hexane) to afford (S)-2-tert-butoxycarbonylamino-4-[3-(4-chloro-phenoxy)-azetidin-1-yl]-4-oxo-butyric acid benzyl ester. [M-BOC] 389.0.

{(S)-3-[3-(4-Chloro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-carbamic acid tert-butyl ester

A solution of (S)-2-tert-butoxycarbonylamino-4-[3-(4-chloro-phenoxy)-azetidin-1-yl]-4-oxo-butyric acid benzyl ester (1.0g, 2.04mmol) in dry THF (10ml) is treated with a 1M solution of lithium aluminium hydride (5.1ml) keeping the temperature between 20-30°C using an ice-water bath. The reaction mixture is stirred at ambient temperature under argon for 2 hours, then quenched by addition of saturated aqueous Na_2SO_4 and filtered through celite. The filtrate is partioned between ethylacetate and saturated brine. The ethylacetate phase dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution

with 5:95 methanol/dichloromethane) to afford {(S)-3-[3-(4-chloro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-carbamic acid tert-butyl ester. [MH]+ 371.0.

(S)-2-Amino-4-[3-(4-chloro-phenoxy)-azetidin-1-yl]-butan-1-ol

A solution of {(S)-3-[3-(4-chloro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-carbamic acid tert-butyl ester. (0.46g, 1.24mmol) in dichloromethane (6ml) is treated with trifluoroacetic acid (2ml) and the reaction mixture stirred for 1 hour at ambient temperature. The solvent is evaporated and the residue dissolved in water. The resulting aqueous solution is basified with saturated aqueous $NaHCO_3$ and extracted into dichloromethane. The dichloromethane is dried over $MgSO_4$ and evporated to afford (S)-2-amino-4-[3-(4-chloro-phenoxy)-azetidin-1-yl]-butan-1-ol as a clear oil. [MH]+ 271.0

1-{(S)-3-[3-(4-Chloro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3,5-dimethoxy-phenyl)-urea

A solution of (S)-2-amino-4-[3-(4-chloro-phenoxy)-azetidin-1-yl]-butan-1-ol (0.2g, 0.74mmol) in dichloromethane (6ml) is treated with 3,5-dimethoxy-phenyl-isocyanate (0.12g, 0.667mmol). The reaction mixture is stirred at ambient temperature for 24hrs and then evaporated. The crude product is purified by flash silica chromatography (elution gradient 3:97 to 7:93 methanol/dichloromethane) to afford 1-{(S)-3-[3-(4-chloro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3-(3,5-dimethoxy-phenyl)-urea. [MH]+ 449.9.

Examples 21, 28, 29, 31 to 33, 35, 38 to 42, 44 to 48 and 50 to 52 are prepared analogously.

1-(3,5-Dimethoxy-phenyl)-3-{(S)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-urea – Example 34

(S)-3-tert-Butoxycarbonylamino-4-(tert-butyl-diphenyl-silanyloxy)-butyric acid benzyl ester

A solution of (S)-3-tert-butoxycarbonylamino-4-hydroxy-butyric acid benzyl ester (1.34g, 4.37mmol) (prepared using the method of Rodriguez, Marc; Linares, Muriel; Doulut, Sylvie; Heitz, Annie; Martinez, Jean ;Tetrahedron Lett. (1991), 32(7), 923-6.) and imidazole (0.88g, 13.01) in dimethylformamide (7ml) is treated with tertbutyldiphenylsilyl chloride (1.69ml, 6.5mmol). The reaction mixture is stirred together at room tempeature for 1 hour, then diluted with water and extracted into ethylacetate. The ethylacetate phase is dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution with 1:1

ethylacetate/hexane) to afford (S)-3-tert-butoxycarbonylamino-4-(tert-butyl-diphenyl-silanyloxy)-butyric acid benzyl ester. [M-BOC] 448.0.

[(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester

A solution of (S)-3-tert-butoxycarbonylamino-4-(tert-butyl-diphenyl-silanyloxy)-butyric acid benzyl ester in (2.37g, 4.33mmol) in dry diethylether (25ml) at 0°C is treated with a 2M solution of lithium borohydride in THF (4.33ml). The reaction mixture is allowed to warm to ambient temperature and stirred for 3 hours under argon, then quenched by addition of water (10ml) and 0.5M aqueous citric acid solution (20ml). The ether is seperated, and the aqueous phase extracted with more ether. The combined ether phases are dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography on a biotage column (90g) (elution with a 1:3 ethylacetate/hexane then methanol) to afford [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester [M-BOC] 344.1.

[(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester

A suspension of polystyrene resin-bound triphenylphosphine (2.33g, 3mmol/g) in dry dichloromethane (25ml) is treated with iodine (1.56g, 6.16mmol) and stirred for 15 minutes under argon . Imidazole (0.477, 7.0mmol) is added and the reaction mixture stirred at room temperature for a further 15 minutes. The reaction mixture is then treated with a solution of [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester (1.24g, 2.8mmol) in dichloromethane (5ml). The reaction mixture is refluxed for 2 hours under argon, then filtered through a celite pad, washing with dichloromethane. The filtrate is washed with 5% aqueous sodium thiosulphate solution and water, dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution with 1:99 methanol/dichloromethane) to afford [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester. [M-BOC] 453.9.

{(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester

A solution of 4-fluorobenzoyl-azetidine hydrochloride (0.192g, 0.892mmol), triethylamine (0.252ml, 3.24mmol) and [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester(0.448g, 0.811mmol) in dimethylformamide (3ml) is stirred at ambient temperature for 18 hours, then partioned between ethylacetate and water. The ethylacetate phase is dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution with a 1:99 methanol/dichloromethane) to afford{(S)-1-(tert-

butyl-diphenyl-silanyloxymethyl)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester. [MH]+ 605.2.

{1-[(S)-3-Amino-4-(tert-butyl-diphenyl-silanyloxy)-butyl]-azetidin-3-yl}-(4-fluoro-phenyl)-methanone

A solution of {(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester. (0.188g, 0.321mmol) in dichloromethane (5ml) is treated with trifluoroacetic acid, and stirred at ambient temperature for 0.5 hour. The reaction mixture is diluted with dichloromethane and washed with water and saturated acqueous $NaHCO_3$. The organic phase is dried over $MgSO_4$ and evaporated to afford {1-[(S)-3-Amino-4-(tert-butyl-diphenyl-silanyloxy)-butyl]-azetidin-3-yl}-(4-fluoro-phenyl)-methanone. [MH]+ 505.2.

1-{(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-propyl}-3-(3,5-dimethoxy-phenyl)-urea

A solution of 1-[(S)-3-amino-4-(tert-butyl-diphenyl-silanyloxy)-butyl]-azetidin-3-yl}-(4-fluoro-phenyl)-methanone (0.152g, 0.301mmol) and 3,5-dimethoxyphenylisocyanate (0.054g, 0.301mmol) in dichloromethane (3ml) is stirred at ambient temperature for 18 hours. The solvent is evaporated and the crude product purified by flash silica chromatography (elution with a 2:98 methanol/dichloromethane) to afford 1-{(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-propyl}-3-(3,5-dimethoxy-phenyl)-urea. [MH]+ 684.1.

1-(3,5-Dimethoxy-phenyl)-3-{(S)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-urea

A solution of 1-{(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-propyl}-3-(3,5-dimethoxy-phenyl)-urea (0.862g, 0.126mmol) in THF (3ml) is treated with a 1M solution of TBAF (0.126ml), and the reaction mixture stirred at ambient temperature for 2 hours. The reaction mixture is partioned between ethylacetate and saturated aqueous $NaHCO_3$. The ethylacetate phase is washed with water and brine, dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution with a 5:95 methanol/dichloromethane) to afford 1-(3,5-dimethoxy-phenyl)-3-{(S)-3-[3-(4-fluoro-benzoyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-urea. [MH]+ 446.1.

Examples 37 and 49 are prepared analogously.

3,4-Dihydro-2H-quinoline-1-carboxylic acid {3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-amide –Example 55

A solution of 1-Bromo-3-isocyanato-propane (0.164g, 1.0mmol) in acetonitrile is stirred with 1,2,3,4-Tetrahydro-quinoline (0.133g, 1.0mmol) and diisopropylethylamine (0.2ml, 1.2mmol). The reaction mixture is stirred for 2 hours at ambient temperature and then the solvent removed. The crude product is taken-up in acetonitrile (4ml) and diisopropylethylamine (0.2ml, 1.2mmol) and 3-(4-Fluoro-phenoxy)-azetidine hydrochloride (0.11g, 1.0mmol) added. The reaction mixture is stirred at ambient temperature for 18 hours, the solvent evaporated and the crude partioned between ethylacetate and saturated sodium bicarbonate solution. The organic phase is washed with brine, dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution gradient ethylacetate then 5:95 methanol/dichloromethane) to afford 3,4-Dihydro-2H-quinoline-1-carboxylic acid {3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-amide. [MH]+ 444.2

1-{3-[3-(4-Fluoro-phenoxy)-azetidin-1-yl]-propyl}-3-(3methoxy-phenyl)-urea – Example 56

{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester

A solution of 3-(4-fluoro-phenoxy)-azetidine hydrochloride (2.0g, 9.85mmol) and diisopropylethylamine (4.28ml, 24mmol) and (3-bromo-propyl)-carbamic acid tert-butyl ester (2.84g, 12mmol) in acetonitrile (20ml) is stirred at ambient temperature for 3 days. The reaction mixture is partioned between dichloromethane and water, the organic phase dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution with a 5:95 methanol/dichloromethane) to afford 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester [MH]+ 325.1.

3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine

A solution of 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester (2.4g, 7.4mmol) in dichloromethane (10ml) is treated with 4M HCl in dioxane (5.7ml), with stirring at ambient temperature. The solvent is evaporated and the residue partioned between dichloromethane and 4M NaOH solution. The dichloromethane phase is dired over $MgSO_4$ and evaporated to afford 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine. [MH]+ 225.0.

1-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-3-(3methoxy-phenyl)-urea

A solution of 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine (0.07g, 0.31mmol) and 1-isocyanato-3-methoxy-benzene (0.041g, 0.31mmol) in dioxane (15ml) is heated to 100°C for 3 hours. The reaction mixture is evaporated and the crude product purified by flash silica chromatography (elution with a 1:9 methanol/dichloromethane) to afford 1-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-3-(3methoxy-phenyl)-urea. [MH]+ 374.0.

Examples 20, 24, 25, 27, 30, 36, 43, 53, 56 and 57 are prepared analogously.

1-(3,4-Difluoro-phenyl)-3-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-urea – Example 23

A solution of 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine (0.04g, 0.178mmol) and 3,4-difluorophenylisocyanate (0.020ml, 0.178mmol) in dichloromethane (1ml) is stirred at room temperature for 5 hours. The solvent is evaporated and the crude product purified by flash silica chromatography (elution gradient a 3:97 to 5:95 methanol/dichloromethane) to afford 1-(3,4-difluoro-phenyl)-3-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-urea. [MH]+ 379.9.

Example 22 is prepared analogously.

1-Cyclohexyl-3-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-1-methyl-urea – Example 54

{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid phenyl ester

A solution of 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine (0.05g, 0.223mmol), phenylchloroformate (0.056ml, 0.446mmol) and dimethylaminopyridine (0.027g, 0.223mmol) in dichloromethane (4ml) is stirred at ambient temperature for 24 hours. The reaction mixture is evaporated and the crude product purified by flash silica chromatography (elution 5:95 methanol/dichloromethane) to afford 3-[3-(4-Fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid phenyl ester. [MH]+ 344.9.

1-Cyclohexyl-3-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-1-methyl-urea

A solution of 3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid phenyl ester (0.035g, 0.101mmol) and N-methylcyclohexylamine (0.02ml, 0.15mmol) in dimethylsulphoxide (1ml) is stirred at ambient temperature for 2 days. The reaction mixture is partioned between ethylacetate and water, the organic phase dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution 5:95 methanol/dichloromethane) to afford 1-cyclohexyl-3-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-1-methyl-urea. [MH]+ 364.0.

2-(3-Acetyl-phenoxy)-N-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-acetamide-Example 10

A solution of (3-acetyl-phenoxy)-acetic acid (0.194g, 1.0mmol) and diisopropylethylamine (0.38g, 3mmol) in dry DMF (3ml) is treated with [dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl-ammonium hexafluoro phosphate (0.38g, 1.0mmol)). After stirring for 5 minutes 3-bromo-propylamine hydrobromide (0.26g, 1.2mmol) is added and stirring continued for a further 40 minutes. The solvent is evaporated and the crude mixture partitioned between ethylacetate and saturated aqueous $NaHCO_3$. The ethyl acetate phase is dried over $MgSO_4$ and evaporated to afford 2-(3-acetyl-phenoxy)-N-(3-bromo-propyl)-acetamide. This crude material is taken up in acetonitrile (3ml) and treated with triethylamine (0.38g, 3mmol) and 3-(4-fluoro-phenoxy)-azetidine hydrochloride (0.11g, 1.2mmol). The reaction mixture is stirred at ambient temperature for 20 hours, the solvent evaporated and the crude product purified by flash silica chromatography (elution 10:90 methanol/dichloromethane) to afford 2-(3-acetyl-phenoxy)-N-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-acetamide. [MH]+ 401.14.

Examples 4, 6 to 13, 16 and 19 are prepared analogously.

Quinoline-3-carboxylic acid {3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-amide - Example 5

Quinoline-3-carboxylic acid (3-bromo-propyl)-amide

A suspension of quinoline-3-carboxylic acid (0.1g, 0.57mmol) in dichloromethane (1.5ml) is treated with dimethylformamide (0.02ml) and then oxalylchloride (0.1ml, 1.15mmol). The reaction mixture is stirred under argon at ambient temperature for 1.6 hours, then evaporated to afford quinoline-3-carbonyl chloride as a crude pale yellow solid. The crude material is suspended in dichloromethane (2.0ml) and treated with bromopropylamine hydrobromide (0.125g, 0.57mmol) and triethylamine (0.42ml, 3mmol). The reaction mixture is stirred at ambient temperature for 3.25 hours, then quenched with water and partitioned between aqueous $NaHCO_3$ solution and dichloromethane. The organic phase is washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution ethyl acetate) to afford quinoline-3-carboxylic acid (3-bromo-propyl)-amide. [MH]+ 292.9.

Quinoline-3-carboxylic acid {3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-amide

This is prepared analogously to Example 10, using quinoline-3-carboxylic acid (3-bromopropyl)-amide in place of 2-(3-acetyl-phenoxy)- N-(3-bromopropyl)-acetamide.

N-{(S)-1-tert-Butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-3,4,5-trimethoxy-benzamide – Example 1

(S)-1-tert-Butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine

A solution of {(S)-1-tert-butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-carbamic acid benzyl ester (0.2g, 0.45mmol) in methanol containing 10% palladium on carbon (66mg) is stirred under an atmosphere of hydrogen for 3 hours, then filtered through celite. The filtrate is evaporated and the residue taken up in ethyl acetate, washed with aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and evaporated to afford (S)-1-tert-butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine, which is used in the following preparation without further purification.

N-{(S)-1-tert-Butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-3,4,5-trimethoxy-benzamide

A solution of 3,4,5-trimethoxy-benzoic acid (0.246g, 1.16mmol) and diisopropylethylamine (0.62ml, 3.47mmol) in dry dimethylformamide (10ml) is treated with [(benzotriazol-1-yloxy)-dimethylamino methylene]-dimethyl-ammonium; tetrafluoro borate (0.32g, 1.0mmol). The reaction mixture is stirred at ambient temperature for 5 minutes, then (S)-1-tert-butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propylamine (0.968mmol) is added and the reaction mixture stirred for 20 hours. The dimethylformamide is evaporated and the residue partitioned between ethylacetate and saturated aqueous $NaHCO_3$. The ethylacetate phase is washed with brine, dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution 50% ethylacetate/hexane to 100%ethylacetate) to afford N-{(S)-1-tert-butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-3,4,5-trimethoxy-benzamide [MH]+ 505.3.

N-{(S)-3-[3-(4-Fluoro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3,4,5-trimethoxy-benzamide

A solution of N-{(S)-1-tert-butoxymethyl-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-3,4,5-trimethoxy-benzamide (0.066g, 0.130mmol) in dichloromethane (2ml) is treated with trifluoroacetic acid (0.11ml, 0.65mmol) and the reaction mixture stirred for 20 hours. The solvent is evaporated and the residue partitioned between ethylacetate and saturated aqueous $NaHCO_3$. The ethylacetate phase is washed with brine, dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution 100%ethylacetate then 5:95 methanol/dichloromethane) to afford N-{(S)-3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-1-hydroxymethyl-propyl}-3,4,5-trimethoxy-benzamide [MH]+ 449.1.

Examples 14 and 15 are prepared analogously.

3-Cyano-N-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-benzenesulfonamide – Example 58

N-(3-Bromo-propyl)-3-cyano-benzenesulfonamide

A suspension of bromopropylamine hydrogen bromide (0.219g, 1mmol) in dichloromethane (2ml) is treated with a solution of dimethylaminopyridine (0.004g) in dichloromethane (0.5ml) followed by a solution of 3-cyano-benzenesulfonyl chloride (0.2g, 1.0mmol) in dichloromethane (0.5ml). Triethylamine (0.3ml, 2.16mmol) is added and the reaction mixture stirred at ambient temperature for 2 hours, then quenched with water and saturated aqueous $NaHCO_3$, and extracted into dichloromethane. The organic phase is washed with aqueous 1M HCl solution and brine, dried over $MgSO_4$ and evaporated to afford crude N-(3-bromo-propyl)-3-cyano-benzenesulfonamide. (^{13}C NMR, 100 MHz, $CDCl_3$, 30.2, 32.6, 41.9, 114.3, 117.5, 130.7, 130.9, 131.1, 136.3, 142.1).

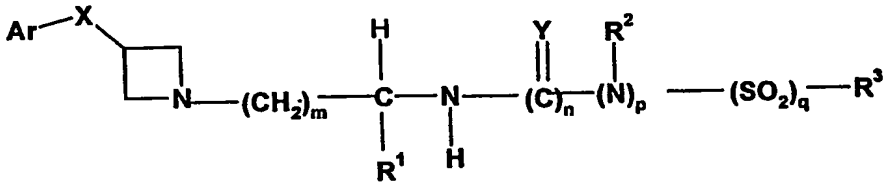
3-Cyano-N-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-benzenesulfonamide

A suspension of 3-(4-fluoro-phenoxy)-azetidine hydrochloride (0.049g, 0.24mmol) in acetonitrile (1.0ml) is treated with the crude N-(3-bromo-propyl)-3-cyano-benzenesulfonamide (0.072g) in acetonitrile (1.0ml) and triethylamine (0.1ml, 0.72mmol). The resulting homogenous reaction mixture is stirred at ambient temperature for 70 hours, the solvent evaporated and the residue partitioned between ethylacetate and aqueous $NaHCO_3$ solution. The ethylacetate phase is washed with brine, dried over $MgSO_4$ and evaporated. The crude product is purified by flash silica chromatography (elution ethylacetate) to afford 3-cyano-N-{3-[3-(4-fluoro-phenoxy)-azetidin-1-yl]-propyl}-benzenesulfonamide. [MH]+ 390.

Examples 59 to 65 are prepared analogously.

Claims

1. A compound of formula



I

in free or salt form, where

Ar is phenyl optionally substituted by one or more substituents selected from halogen, C_1-C_8-alkyl, cyano or nitro,

R^1 is hydrogen or C_1-C_8-alkyl optionally substituted by hydroxy, C_1-C_8-alkoxy, acyloxy, halogen, carboxy, C_1-C_8-alkoxycarbonyl, -$N(R^4)R^5$, -$CON(R^6)R^7$ or by a monovalent cyclic organic group having 3 to 15 atoms in the ring system,

R^2 is hydrogen or C_1-C_8-alkyl and R^3 is C_1-C_8-alkyl substituted by phenyl, phenoxy, acyloxy or naphthyl, or R^3 is C_3-C_8-cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms, phenyl or naphthyl, said phenyl, phenoxy or naphthyl groups being optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, acyl, nitro, C_1-C_8-alkyl, C_1-C_8-haloalkyl, C_1-C_8-alkoxy, C_1-C_8-haloalkoxy, C_1-C_8-alkylthio, C_1-C_8-alkoxycarbonyl, acylamino, C_1-C_8-alkylamino, di(C_1-C_8-alkyl)amino or di(C_1-C_8-alkyl)aminocarbonylmethoxy, or R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which 1, 2 or 3 are hetero atoms,

R^4 and R^5 are each independently hydrogen or C_1-C_8-alkyl, or R^4 is hydrogen and R^5 is hydroxy-C_1-C_8-alkyl, acyl, $-SO_2R^8$ or $-CON(R^6)R^7$, or R^4 and R^5together with the nitrogen atom to which they are attached denote a 5-or 6-membered heterocyclic group,

R^6 and R^7 are each independently hydrogen or C_1-C_8-alkyl, or R^6 and R^7 together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group,

R^8 is C_1-C_8-alkyl, C_1-C_8-haloalkyl, or phenyl optionally substituted by C_1-C_8-alkyl,

X is $-C(=O)-$, -O-, $-CH_2-$, or CH(OH),

Y is oxygen or sulfur,

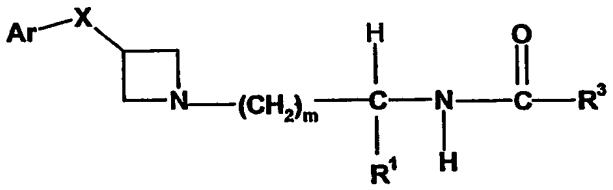
m is 1, 2, 3 or 4, and

n, p and q are each 0 or 1, n+p+q=1 or 2, n+q=1, p+q=1, and when n is 0, p is 0.

2. A compound according to claim 1, in which

Ar is phenyl substituted by one or two substituents selected from fluorine and chlorine,
R^1 is hydrogen, C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy, C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or C_1-C_4-alkyl substituted by naphthyl,
R^2 is hydrogen or C_1-C_4-alkyl, and R^3 is C_1-C_4-alkyl substituted by phenyl or phenoxy, or C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or C_1-C_4-alkyl substituted by naphthyl, or R^3 is C_5-C_8-cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which one or two are hetero atoms, selected from nitrogen, oxygen or sulfur, phenyl or naphthyl, said phenyl, phenoxy and naphthyl groups being optionally substituted by one, two or three substituents selected from halogen, cyano, nitro, hydroxy, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl, C_1-C_4-alkylthio, di(C_1-C_4-alkyl)amino or C_1-C_4-alkylcarbonylamino, or R^2 and R^3, together with the nitrogen atom to which they are attached, denote a heterocyclic group having a N-heterocyclic ring optionally fused to a benzene ring.
X is –O-, -C(=O)- or -CH_2-,
Y is oxygen and
m is 2, 3 or 4.

3. A compound according to claim 1, which is of formula



II

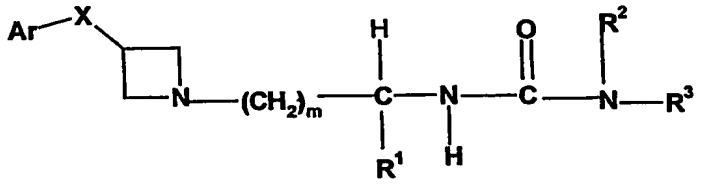
where
Ar is phenyl substituted by one or two substituents selected from fluorine and chlorine, one of said substituents being para to the indicated group X,
R^1 is hydrogen, C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy, C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or C_1-C_4-alkyl substituted by naphthyl,

R^3 is phenyl substituted by one, two or three substituents selected from halogen, cyano, di(C_1-C_4-alkyl)amino, C_1-C_4-alkylcarbonylamino, C_1-C_4-alkoxy, or R^3 is naphthyl optionally substituted by fluorine, or R^3 is C_1-C_4-alkyl substituted by phenoxy which is optionally substituted by one or two substituents selected from halogen, cyano, C_1-C_4-alkyl, C_1-C_4-alkoxy or C_1-C_4-alkylcarbonyl, or R^3 is C_1-C_4-alkyl substituted by benzoyloxy or phenoxy-C_1-C_4-alkylcarbonyloxy which are optionally substituted in the benzene ring by at least one substituent selected from C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl and aminosulfonyl, or R^3 is a heterocyclic group having a 5- or 6-membered heterocyclic ring in which one or two ring atoms are hetero atoms selected from nitrogen, oxygen and sulfur optionally fused to a benzene ring which is optionally substituted by one or two substituents selected from halogen, C_1-C_4-alkoxy and C_1-C_4-alkylcarbonyl,

X is –O-, and

m is 2 or 3.

4. A compound according to claim 1, which is of formula



III

where

Ar is phenyl substituted by one or two substituents selected from fluorine and chlorine, one of said substituents being para to the indicated group X,

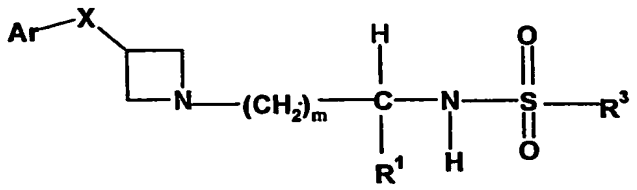
R^1 is hydrogen, C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy,

R^2 is hydrogen or C_1-C_4-alkyl and R^3 is C_5-C_9-cycloalkyl, a heterocyclic group having 5 to 11 ring atoms of which one or two are nitrogen or oxygen atoms, phenyl optionally substituted by one, two or three substituents selected from fluorine, chlorine, hydroxy, nitro, C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxy, phenyl-C_1-C_4-alkyl substituted in the phenyl group by one or two substituents selected from halogen and C_1-C_4-alkyl, C_1-C_4-alkyl substituted by naphthyl, or C_5-C_6-cycloalkyl having a benzo group fused thereto, or R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group having a 6-membered N-heterocyclic ring fused to a benzene ring which is optionally substituted by up to 2 C_1-C_4-alkoxy groups,

X is –O- or –C(=O)-, and

m is 2 or 3.

5. A compound according to claim 1, which is of formula



IV

where

Ar^1 is phenyl substituted by one or two substituents selected from fluorine and chlorine, one of said substituents being para to the indicated group X,

R^1 is hydrogen or C_1-C_4-alkyl substituted by hydroxy or C_1-C_4-alkoxy,

R^3 is phenyl optionally substituted by halogen, C_1-C_4-alkyl or cyano, or R^3 is an aromatic N- or S-heterocyclic group having 5 to 10 ring atoms, or R^3 is phenyl-C_1-C_4-alkyl,

X is –O- and

m is 2 or 3.

6. A compound according to claim 1 substantially as described in any one of the Examples.

7. A compound according to any one of the preceding claims for use as a pharmaceutical.

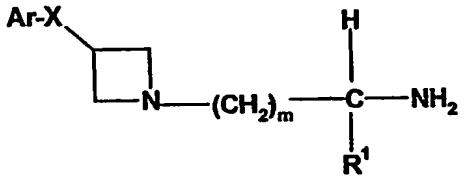
8. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 6.

9. The use of a compound according to any one of claims 1 to 6 for the manufacture of a medicament for the treatment of a condition mediated by CCR-3.

10. Use according to claim 9, in which the condition is an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

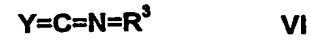
11. A process for the preparation of a compound of formula I which comprises

(i) (A) for the preparation of compounds of formula I where n is 1 and p is 1, reacting a compound of formula



V

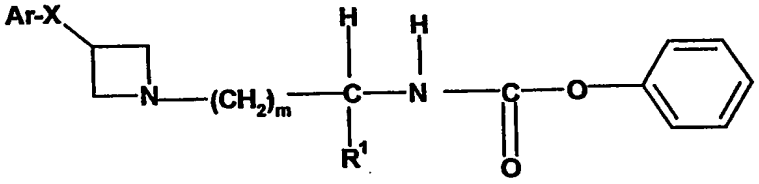
with a compound of formula



VI

where Ar, R^1, R^3, X, Y and m are as hereinbefore defined, with the proviso that when R^1 contains a reactive functional group it may be in protected form, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen, or

(B) for the preparation of a compound of formula I where n is 1, p is 1 and R^2 is hydrogen or C_1-C_8-alkyl, reacting a compound of formula



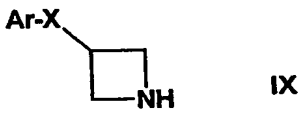
VII

with a compound of formula

VIII

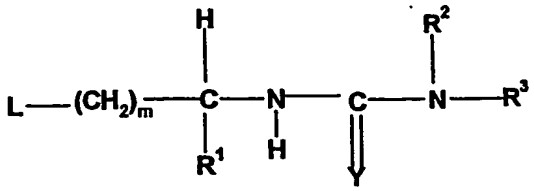
where Ar, R^1, R^2, R^3 and m are as hereinbefore defined, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen, or

(C) for the preparation of a compound of formula I where n is 1, p is 1 and R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group, reacting a compound of formula



IX

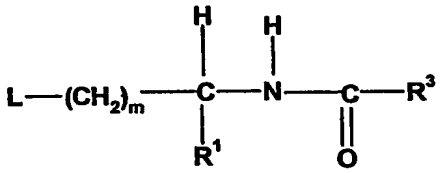
with a compound of formula



X

where Ar, R^1, Y and m are as hereinbefore defined, R^2 and R^3 together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which one, two or three are hetero atoms, and L is halogen, preferably bromine, or

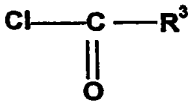
(D) for the preparation of a compound of formula I when n is 1, p is 0, R^2 is hydrogen and Y is oxygen, reacting a compound of formula IX with a compound of formula



XI

where R^1, R^3, L and m are as hereinbefore defined, or

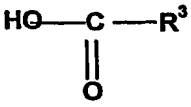
(E) for the preparation of a compound of formula I where n is 1, p is 0, R^2 is hydrogen and Y is oxygen, reacting a compound of formula V with a compound of formula



XII

where R^3 is as hereinbefore defined, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen, or

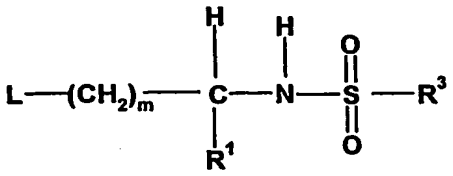
(F) for the preparation of a compound of formula I where n is 1, p is 0, R^2 is hydrogen and Y is oxygen, reacting a compound of formula V with a compound of formula



XIII

where R^3 is as hereinbefore defined, and, where R^1 in the product contains a protected functional group, replacing the protecting group by hydrogen or

(G) for the preparation of a compound of formula I where n is 0, p is 0, and q is 1, reacting a compound of formula IX in the form of a hydrohalide salt with a compound of formula



XIV

where R^1, R^3, L and M are as hereinbefore defined, and

(ii) recovering the product in free or salt form.